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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,204	01/24/2001	Malcolm R. Alison	54113-8004.US01	4799

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/769,204	ALISON ET AL.
Examiner	**Art Unit**
Daniel M Sullivan	1636

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *26,27 and 51* is/are allowed.

6)☒ Claim(s) *28-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *12*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

This Office Action is a response to the "Amendment and Response" filed 25 November 2002 (Paper No. 11) in reply to the Non-Final Office Action mailed 24 August 2002 (Paper No. 9). Claims 26-51 were considered in Paper No. 9. Claims 28, 35 and 51 were amended in Paper No. 11. Claims 26-51 are currently pending and under consideration.

Oath/Declaration

The requirement for a new oath is withdrawn.

Response to Amendment

35 U.S.C. § 112, first paragraph

Rejection of claim 51 under 35 U.S.C. § 112, first paragraph, as lacking enablement is withdrawn in view of the amendments to the claim in Paper No. 11.

Claims 28-50 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for reasons of record and set forth herein below.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28 and 35, and claims 29-34 and 36-50 as they depend from claims 28 or 35, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended claims 28 and 35 such that they are now limited to a method of treating "diseases directly affecting liver function". There is no support for this limitation in the disclosure as originally filed. In the response, Applicant does not point to a specific recitation of this limitation in the original disclosure and merely states, "a list of many of the diseases that directly affect liver function is found on pages 18 and 19" (fourth paragraph on page 5). However, no such genus as "diseases directly affecting liver function" is described in the original specification or claims, and nothing in the disclosure or amendment specifically limits the claim to treatment of only those diseases identified in the specification. Therefore, the amended claims are not adequately supported by the originally filed application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28 and 35, and claims 29-34 and 36-50 as they depend from claims 28 or 35, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in being directed to a method of treating diseases "directly affecting liver function". The metes and bounds of the claimed subject matter are unclear

because the disclosure does not define the meaning of "directly affecting liver function". Applicant provides that the list of diseases on page 18 and 19 of the specification is comprised within the genus of diseases directly affecting liver function. However, given the diversity of conditions on this list, it is not possible to ascertain what conditions would be excluded from diseases directly affecting liver function. Furthermore, although Applicant presumably feels that the claims are now more narrow in scope than claims directed to a method of treating diseases "associated with the liver", it is not possible to determine how the scope of the claims has changed because it appears that Applicant is relying on the same set of conditions to delimit both phrases. Therefore, the scope of the amended claims is indefinite.

Response to Arguments

In response to the Examiner's arguments set forth in the previous Office Action, Applicant first argues that the reduction to practice of the invention described in the specification "merely serves to show that the expression of the gene in the vector is occurring and also allows for measuring the efficacy of transfection" and asserts, "any RNA, protein, or polypeptide which can be expressed in liver cells using vectors, can experience expression with the concurrent administration of T3 and HGF" (paragraph bridging pages 5 and 6). Applicant's point is taken insofar as the invention is directed to improving the efficiency of *in vivo* liver cell retroviral transduction. However, Claims 28-50 are directed to a method of treating a disease and the basis of the enablement rejection is the unpredictability of obtaining expression of therapeutically relevant degree and duration. Given the many obstacles to obtaining effective treatment using gene therapy techniques described in the previous Office Actions, the skilled artisan would not

predict success in treating a diverse set of diseases based on a showing of improved expression of a non-therapeutic protein.

Applicant also points out that claim 11 of U.S. Patent 6,248,725 is similar to the instant claims and states, [t]he fact that the parent application issued with a claim containing language that is similar to the rejected language in the present application should be persuasive to allow the claims..." This is not persuasive, however, because the critical difference between the instant rejected claims and the patented claim is that the patented claim is directed to "[a] method for improving the efficiency of *in vivo* liver cell retroviral transduction" while the instant rejected claims are directed to a method of treating comprising *in vivo* gene transfer. As the instant claims are directed to a method of treatment, the enabling disclosure must teach how to treat a disease using the claimed method. Claim 11 of '725 is actually most similar to the instant claims 26 and 27, which are allowed.

Applicant, next argues that the instant claims are enabled for any disease in which proliferation of liver cells and/or expression of a gene product in liver cells is therapeutically effective, stating, "[j]ust because an invention has broad applicability does not mean that Applicants must list every potential disease that could be treated by the invention" (paragraph bridging pages 6 and 7). This is not persuasive because, as pointed out in the previous office actions, therapeutic efficacy is unpredictable in the art of gene therapy. Although it is conceivable that once the many problems now facing the field of gene therapy are overcome the instant method could be used to treat a variety of diseases, the amount of experimentation required to overcome the obstacles to effective gene therapy at the time the instant application was filed was well beyond what could be accomplished by routine experimentation.

In response to the Examiner's assertion that the specification does not disclose how the increased transduction levels would lead to treatment, Applicant argues that the specification lists some potential RNAs, proteins and polypeptides and leaves it up to the skilled practitioner to assess the liver-related disease and decide what product or products the proliferating liver cells should produce to ameliorate the condition. This argument is not persuasive because teachings from the gene therapy art such as those of Davern *et al.* cited in previous office actions, show that the problems associated with obtaining effective gene therapy go well beyond deciding which gene to use. The task characterized by Davern *et al.* as "Herculean" is not selecting an appropriate transgene, it is "to reprogram the genetic code of genetically impaired cells".

Next, Applicant cites arguments in the previous Amendment, filed 17 June 2002, regarding the utility of the rat as a models for translation to human subjects. This is not persuasive because none of the cited references teach the translation of findings obtained in rats to successful gene therapy in humans. Although the cited art suggests that rats are good models of human disease, until there is some evidence that gene therapy of rats can be translated into success in the clinic the skilled artisan has no basis to expect success in treating humans with gene therapy based on findings obtained in rats.

In response to the Examiner's assertion that there is insufficient guidance provided by the specification for parameters affecting delivery and expression of therapeutic amounts of DNA in the cells, Applicant points to teachings in the specification relating to the administration of KGF and T3 as evidence that the specification gives direction on how to make and use the present invention. This argument is not persuasive because the teachings of the specification stop well short of demonstrating therapeutic efficacy in an animal model, let alone a human, therefore

Applicant is relying on the teachings of the relevant art to enable the claims beyond expression of a reporter gene. However, as pointed out in the previous office actions, the teachings of the prior art are not enabling for the full scope of the claimed subject matter because they do not teach the skilled artisan how to use the instant method to treat any disease directly affecting liver function.

In support of the predictability of gene therapy, Applicant again cites which Davern *et al.* who states, "...we anticipate accelerating progress towards the clinical application of gene therapy for liver disease". However, this statement immediately follows the characterization of the aim of gene therapy by Davern *et al.* as Herculean. Applicant is reminded that the test of enablement is whether the skilled artisan would be able to make or use the claimed invention without undue experimentation. Clearly Davern *et al.* is not teaching that only routine experimentation will be required to bring the promise of gene therapy to fruition. On the contrary, Davern *et al.* is teaching that successful gene therapy can be envisioned in spite of the tremendous amount of work that lies ahead.

Applicant also cites the teachings of Fujimoto *et al.* (1999) and Ueki *et al.* (2000) as proof that "gene therapy techniques are generally being widely applied and the impact and possibility for gene therapy extends beyond the specific products produced in those experiments" (second paragraph on page 9). However, Fujimoto *et al.* characterizes the significance of their findings this way: "Using these newly developed methods, HGF gene therapy *may eventually* be applied clinically for the patients with liver cirrhosis" (final paragraph on page D35; emphasis added), and Ueki *et al.* characterize the significance of their findings this way: "transduction of skeletal muscles with HGF genes as presented here *may eventually* be translated into a useful

clinical regimen of gene therapy for the treatment of patients with progressive liver cirrhosis" (paragraph bridging columns 1 and 2 on page 228; emphasis added). Thus, neither Fujimoto *et al.* nor Ueki *et al.* express any belief that their findings support gene therapy of any liver disease other than cirrhosis, and the statements from both Fujimoto *et al.* and Ueki *et al.* regarding the likelihood of translating their findings to the clinic are guarded. Thus, far from teaching that gene therapy, as of 1999, was being generally and widely applied, Fujimoto *et al.* and Ueki *et al.* express some skepticism that success in an animal model can be translated to success in treating the same disease in humans, let alone every disease that affects the same organ.

Finally, Applicant argues, because "the present invention significantly increases the successful transduction of a given gene in a liver cell…[and] none of the other gene therapy methods in the literature discuss these stimulating factors as part of their parameters, it is not accurate to compare those methods to the present method" (first paragraph on page 10). This argument is not persuasive because the teachings of the prior art are relied upon to show the degree to which practicing the claimed method was unpredictable and the level of experimentation required to use the invention commensurate with the full scope of the claims. The Examiner's assertion is that the teachings of the prior art demonstrate that the problems facing the skilled artisan seeking to use the claimed invention could not be overcome by merely increasing successful transduction of any given gene in a liver cell. Thus the teachings of the instant disclosure and prior art would not enable the skilled artisan to practice the full scope of the claimed subject matter without first engaging in undue experimentation.

Allowable Subject Matter

Claims 26, 27 and 51 are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
February 5, 2003

JAMES KETTER
PRIMARY EXAMINER